Effects of vitamin E administration on APACHE II Score in ARDS patients

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ABSTRACT

Background and purpose of the study: The acute respiratory distress syndrome (ARDS) is a common clinical disorder caused by injury to the alveolar epithelial and endothelial barriers of lung. In ARDS patients, oxidative stress is increased and plasma antioxidant levels are reduced. Vitamin E has an important role in antioxidant defense mechanisms. In this study the effect of vitamin E on decrease of APACHE II score in ARDS patients was investigated.

Materials and methods: Twenty patients [mean (SE): age = 51.2 ± 6.41 years] with ARDS were enrolled. After diagnosis based on inclusion and exclusion criteria, ten patients as treatment group received 600 IU vitamin E daily intramuscularly. Control group received normal saline as placebo. Plasma samples and Acute Physiology and Chronic Health Evaluation (APACHE) II score were obtained before administration, 4hrs and 12hrs after each intervention and repeated three days for each patient. Results were analyzed by use of an SPSS software package with a repeated-measures analysis of variance (ANOVA).

Results: Significant changes were observed in APACHE II score from first to seventh measurement (p=0.0001) in treatment group, but vitamin E concentration altered significantly in only first to seventh measurement (p= 0.019).

Conclusion: From the results of this study, it seems that the use of vitamin E as a lipid-soluble antioxidant along with other supportive measures is beneficial in decreasing APACHE II score in ARDS patients.

Keywords: Acute respiratory distress syndrome, Vitamin E, APACHE II score, Oxidative stress

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) is an acute lung dysfunction associated with a variety of diseases, such as pneumonia, shock, sepsis and trauma. The shortness of breath and hypoxemia are the two major problems in the ARDS patients due to respiratory failure ($Pa_{O2}/Fi_{O2}<200$) (1). Recent estimates of acute respiratory distress syndrome (ARDS) incidence in the United State have varied from 1.3 to 22 per 100,000 person years (2).

Supportive oxygen therapy, pulmonary inflammation, and nutritional inadequacies are usually occurred in ARDS patient, so oxidative stress is one of the major problems in these patients (3, 4) and antioxidant therapy is a necessary intervention (5). Enzymatic and non enzymatic antioxidants such as vitamin E normally neutralize the free radicals, but in patients who require intensive care, a decrease in removal or an over production of the radicals occurs and oxygen free radicals become a problem (6). Therefore the antioxidants with ideal concentrations at the right place and time should be administered in intensive care patients with acute inflammation (7). It has been known for some times that circulating vitamin E, the primary lipid-soluble antioxidant, is low in critically ill patients (8-10), and the effect of enteral vitamin E supplementation have been studied in various investigations (11, 12), but there is no report on effects of parenteral vitamin E on ARDS patients. This study was designed to evaluate the effect of parentral vitamin E on APACHE II Score in

ARDS patient and the vitamin E concentration was also determined.

MATERIAL AND METHODS

Subjects and sample collection
Over 12-month period, 20 patients meeting criteria for ARDS (see the subsequent discussion) were recruited from general ICU at Sina hospital, a teaching hospital of Tehran University of Medical Science (TUMS) and a major referral center in Tehran, Iran. The study was a randomized, open lable, prospective and placebo controlled trial with ten patients as treatment group and the other ten patients as control. These patients were about 20% of all mechanically ventilated patients with multiple trauma, cerebral vascular accident (CVA), and myocardial infarction. In addition no patient received nitric oxide (NO), surfactants, N- acetyl cystein (NAC) or other experimental pharmacological intervention for Acute Long Injury (ALI), ARDS or sepsis. Treatment group during three days of study received 600 IU/day vitamin E, and at the same time control group received normal saline as placebo. Ethical approval for the study was obtained from Tehran University of Medical Science (TUMS) and all subjects or their relatives were informed and singed a written consent prior taking part in the study.

Criteria for diagnosis of ALI and ARDS
The criteria for diagnosis of ALI and ARDS as set by the north American/European Consensus (1) was adapted as follows: acute onset of lung injury, diffuse bilateral infiltrates in chest radiography, $PaO_2/FiO_2 < 200$ mmHg for ARDS and $PaO_2/FiO_2 < 300$ mmHg for ALI, or no clinical evidence of congestive heart failure (CHF) and patients using PEEP (Positive End Expiratory Pressure).
Exclusion criteria consisted of renal failure; liver dysfunction; increase in P/F; extubation of patients, platelet count less than 100,000, mean arterial pressure less than 65 mmHg and patient death during the study.

Data collection
During mechanical ventilation, the laboratory and ventilator variables were recorded. Each patient was followed for three days and received 600 IU vitamin E daily as single dose. The APACHE II Score (13) and plasma vitamin E concentration were measured at the base line, 4hrs and 12hrs after each vitamin E administration (seven records for each patient). Patient screening, data collection and chest radiograph interpretation were performed by investigators.

Experimental procedure
Plasma samples were stored at -80°C until analyses. Vitamin E was measured, after extraction with methanol, by HPLC equipped with UV detector at 294 nm. Methanol, deionized water and buthanol (90: 4: 6) was used as mobile phase and the column was Eurospher 100 C_8 (4.6 mm×25cm). The flow rate was set at 1.0 ml/min and α- tochopherol acetate was used as internal standard.

Statistical analysis
Results were expressed as mean ± SEM and analyzed by the use of an SPSS software package (version 11.5) with a repeated-measures analysis of variance (ANOVA).

RESULTS

During this study, 158 patients were admitted to the ICU, of these, 138 met the pre-defined exclusion criteria at the time of randomization and were withdrawn from the study shortly after enrollment, resulting in a study population of 20 patients. Ten patients were randomized to the treatment group and the other half to control group. There were 13 men and 7 women, aged 50.0 ± 3.93 yr (mean ± SEM; range 21 to 78 yr). Both groups received standard supportive measures for critically ill patients. A defined primary comorbid condition was often present, including multiple trauma (n = 9; 45%), CVA (n = 2; 10%), gastric cancer (n = 1; 5%), sepsis (n = 2; 10%), aspiration pneumonia (n=2; 10%), pancreatitis (n=2; 10%) and myocardial infarction (n = 2; 10%). Demographic and clinical data of all patients are shown in Table 1. No significant difference was observed in plasma vitamin E concentration, APACHE II score and other important variables between treatment and control group at base line, indicating similarity of these groups (Table 1). In twenty patients the inclusion criteria of Maunchly's test statistic for sphericity was non significant (i.e. p=0.147 > 0.05), so it is reasonable to conclude that the variances of differences are not significantly different and are roughly equal. Test of between-subject effect (control to treatment group) showed a p value of 0.84, but in treatment group pair wise comparisons showed that the APACHE II score of baseline is significantly different in second and third day 4hrs and 12hrs after each vitamin E administration (p= 0.007, 0.0001, 0.0001, 0.0001 respectively) and significant changes were observed in APACHE II score over time. On the other hand the Vitamin E concentration altered significantly in only first to seventh measurement (p= 0.019) for treatment group (Figure 1). The lines for the two groups for APACHE II score are

Table 1. Base line patient characteristics comparing treatment with control group

	Treatment	Control	p Value
Age, yr	51.20±6.41	48.80±4.88	0.769
Women/men	4/6	3/7	0.500
ALI/ARDS	4/6	5/5	0.64
APACHE II Score	22.20±1.33	22.50±1.01	0.860
PaO_2/FiO_2	176.60±19.35	192.00±15.681	0.544
Vitamin E, mcg/ml	2.198±0.426	2.799±0.506	0.376

Data are expressed as mean ± SEM.
ALI: Acute Lung Injury; ARDS: Adult Respiratory Distress Syndrome; APACHE: Acute Physiology And Chronic Health Evaluation; PaO_2: Pressure of Arterial Oxygen; FiO_2: Fraction of Inspired Oxygen.
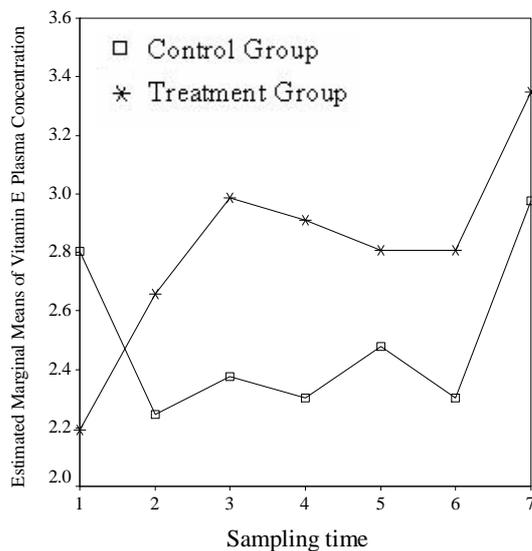

Figure 1. The Mean of Vitamin E concentration in control and treatment groups versus sampling times
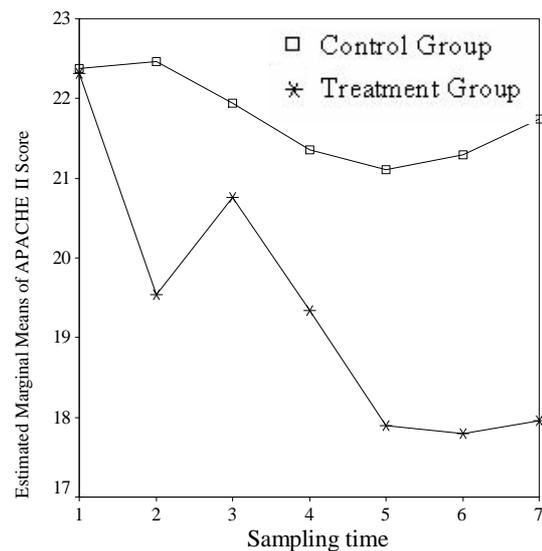

Figure 2. The Mean of APACHE II Score in control and treatment groups versus sampling times

rather far apart (Figure 2) and the within subject test indicated that there is a significant time effect (p=0.001, power = 0.975) and the interaction of time and group is also significant (p=0.016, power=0.711).

DISCUSSION

Acute lung injury (ALI) and its most severe form, the acute respiratory distress syndrome (ARDS) are frequent complications in critically ill patients and responsible for significant mortality and morbidity (14). Lipids constitute about 90% of the alveolar surfactant and are extremely sensitive to oxidants (15). Therefore the lipophilic antioxidants should play a special role in protection of the lung. Since the most important lipophilic antioxidant in the lung is vitamin E (16), this study was designed to determine the protective effect of vitamin E supplementation in ARDS which is the most important lung injury. During the past decades several studies of antioxidant therapy in critically ill patients (12,

17) have been carried out but results varied because of factors such as means of supplementation and analysis of plasma samples. Usually the method of vitamin E administration was enteral feeding, but it seems that IM administration would be a suitable method for supplementation and the plasma vitamin E level is also a useful parameter for measurement of vitamin E status in healthy volunteer (18). Mean vitamin E concentration in all patients at base line was 2.50 ± 0.33 which shows a significant defect compared with minimum allowance of vitamin E concentration in normal subjects (18), indicating critical need for vitamin E supplementation in these patients. Since in ARDS patients, oxidative stress markers are elevated several- fold (19, 20), therefore much higher physiological requirement of vitamin E is needed and this vitamin might be reached quickly to oxygen supply dependent organs. In this study each patient in treatment group received 600 IU vitamin E in single dose daily. The increase in vitamin E concentration

was not found to be significant during the first measurements, but altered significantly in only first to seventh measurement (p= 0.019) for treatment group (Figure 1). It seems that continuation of vitamin E administration could be useful during the high concentration of oxygen therapy (FiO$_2\geq$50%), but dosing adjustment of the vitamin E must be considered due to an increase in intrathoracic pressure, decrease in cardiac output accompanied by the use of mechanical ventilation. On the other hand as the main part of superoxide dismutase enzyme is vitamin E, it could be assumed that antioxidant effect of this vitamin may not be dependent on its plasma concentration. Previous finding have shown that there is a significant increase in alveolar vitamin E concentration in ARDS patients despite of a decrease in plasma concentration (21), perhaps the bronco-alveolar fluid is a better predictor for vitamin E estimation in these patients. In this study the hypothesis that vitamin E administration would influence the APACHE II Score was analysed by repeated measure ANOVA through different days. The lines for the two groups of APACHE II score were rather far apart (Figure 2) and the within subject test indicate that there is a significant time effect (p=0.001, power = 0.975). In other words, routine treatment protocol improved the situation in both groups by time, but treatment group recovery (As seen as its slope) was better. Statistically this is indicated in interaction of time and group significance (p=0.016, power=0.711) which means that the groups are changing over time but are changing in different slopes. In treatment group pair wise comparisons showed that the APACHE II Score of baseline is significantly different in second and third day at 4 hrs and 12 hrs after each vitamin E administration (p= 0.007, 0.0001, 0.0001, 0.0001 respectively) and significant changes were observed in APACHE II Score over time. Therefore it may be concluded that use of vitamin E as a lipid-soluble antioxidant along with other supportive measures is beneficial in decreasing APACHE II Score in ARDS patients. In the previous report (22) it was shown that patients with ARDS are in a deficient antioxidant status and NAC treatment can successfully improve intracellular GSH and enhance overall antioxidant power and outcome of patients. Taken together, the current results suggest that the severity of the disease process in ICU patients might be decreased with vitamin E supplementation, but further study is necessary to investigate the mechanism of vitamin E action in ARDS patients under the conditions of oxidative stress along with other supportive measures.

ACKNOWLEDGMENTS

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